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Appln. Trans.
PATENT

A

UTILITY PATENT
APPLICATION
TRANSMITTAL

(Only for new nonprovisional
applications under 37 CFR 1.53(b))

Attorney Docket No. 31064A

First Named Inventor Podos et al.

Express Mail Label No. EE657555936US

Total Pages 3

May 6, 1998

BY EXPRESS MAIL - Label No. EE657555936US

Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

Sir:

Enclosed herewith for filing is a patent application of Podos et al. entitled 8-ISO-PROSTAGLANDINS
FOR GLAUCOMA THERAPY

which includes:

<input checked="" type="checkbox"/> Specification	<u>13</u> Total Pages
<input checked="" type="checkbox"/> Claims	<u>5</u> Total Pages
<input checked="" type="checkbox"/> Abstract	<u>1</u> Total Pages
<input type="checkbox"/> Drawing(s)	<u>0</u> Total Sheets
<u> </u> formal	
<u> </u> informal	

☒ Combined Declaration and Power of Attorney (UNEXECUTED) 3 Total Pages
☐ Newly executed (original or copy)
☐ Copy from a prior application
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If a continuing application, check appropriate box:

☐ Continuation ☐ Divisional ☒ Continuation-In-Part (CIP)
of prior application No.

☒ Amend the specification by inserting, before the first line, the following sentence:

"This is a ☐ continuation ☐ divisional ☒ continuation-in-part
of copending application Serial No. 08/853,803 filed May 9, 1997."

Attorney Docket No. 31064A

- ☒ An Assignment of the invention to _.
- ☐ is attached. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
- ☒ will follow.
- ☐ has been filed in the prior application
- ☐ Small Entity Statement(s)
- ☐ Small Entity Statement filed in prior application. Status still proper and desired.
- ☐ Information Disclosure Statement (IDS) PTO-1449
- ☐ Copies of IDS Citations.
- ☐ Preliminary Amendment
- ☒ Return Receipt Postcard
- ☐ Other _
- ☐ Cancel in this application original claims _ of the prior application before calculating the filing fee.

The filing fee has been calculated as shown below:

FOR	(Col. 1)		(Col. 2)		Small Entity		OR	Other Than A	
	No. Filed		No. Extra		Rate	Fee		Rate	Fee
Basic Fee									\$790
Total Claims	21	-20	=	10	x \$11=	\$0		x \$22 =	\$22
Ind. Claims		-3	=	0	x \$41 =	\$0		x \$82 =	\$0
Multiple Dependent Claim					+ \$135 =	\$0		+\$270=	\$0
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- ☒ Basic filing fee \$812.00
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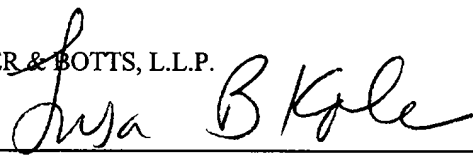
Attorney Docket No. 31064A

Priority

- ☐ Priority of application Country __, Appln. No. __ filed __ is claimed under 35 U.S.C. 119.
- ☐ Certified Copy of Priority Document(s) Country __, Appln No. __, filed __.
- ☐ is/are attached ☐ will follow ☐ has been filed in the parent application S/N __.
- ☒ The Commissioner is hereby authorized to charge payment of any additional filing fees required under 37 CFR 1.16, 1.17, and 1.21(h) associated with this communication or credit any overpayment to Deposit Account No. 02-4377. Two copies of this sheet are enclosed.

BAKER & BOTTS, L.L.P.

By


Richard S. Clark
PTO Reg. No. 26,154

Lisa B. Kole
PTO Reg. No. 35,225

Enclosures

BAKER & BOTTS, L.L.P.

30 ROCKEFELLER PLAZA

NEW YORK, NEW YORK 10112

TO ALL WHOM IT MAY CONCERN:

Be it known that WE, STEVEN M. PODOS, THOMAS W. MITTAG and BERNARD BECKER, citizens of U.S.A., U.S.A. and U.S.A. , residing in Tenaflly, Pleasantville and University City , County of Bergen, Westchester and St. Louis , State of New Jersey, New York and Missouri whose post office addresses are 2 Knoll Road, Tenaflly, New Jersey 07670, 167 Woodland Drive, Pleasantville, New York 10570 and 8655 West Kingsbury, St. Louis, Missouri 63124 (respectively,) have invented an improvement in

8-ISO-PROSTAGLANDINS FOR GLAUCOMA THERAPY

of which the following is a

SPECIFICATION

INTRODUCTION

The present invention relates to the use of 8-iso prostaglandins and their derivatives for decreasing intraocular pressure, for example in the treatment of glaucoma. It is based, at least in part, on the discovery that 8-iso prostaglandin E₂ effectively decreased intraocular pressure by a trabecular meshwork outflow mechanism.

BACKGROUND OF THE INVENTION

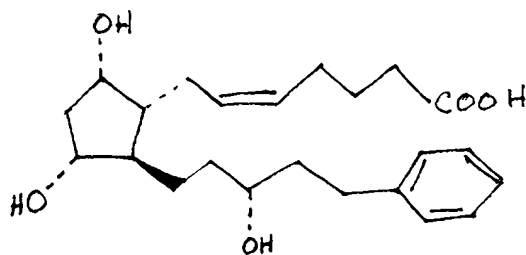
Glaucoma is a major eye disease which can cause progressive loss of vision leading to blindness. The majority of human glaucomas are associated with increased intraocular pressure ("IOP") resulting from an imbalance in the rate of secretion of aqueous humor by the ciliary epithelium into the anterior and posterior chambers of the eye and the rate of aqueous humor outflow from these chambers, primarily via the canal of Schlemm. High IOP is considered the major risk factor for glaucomatous visual impairment resulting from the death of retinal ganglion cells, loss of the nerve fiber layer in the retina, and destruction of the axons of the optic nerve. Current treatments are directed toward reducing intraocular pressure.

Glaucoma is typically classified, on the basis of its etiology, as primary or secondary. Primary glaucoma in adults, a disorder in which the underlying cause is poorly understood, is associated with increased IOP due to an obstruction of aqueous humor outflow . The obstruction may be caused by a blockage located at the angle formed between the iris and the lateral cornea, categorized as either open angle or acute or chronic angle closure. The anterior chamber of the eye appears normal in chronic open angle glaucoma, despite impaired drainage of aqueous humor. In contrast, the anterior chamber is shallow and the filtration angle is narrowed in chronic angle-closure glaucoma, wherein the trabecular meshwork and the canal of Schlemm may be obstructed by the iris. An acute attack of glaucoma may arise in this context when the pupil dilates, pushing the root of the iris forward to block the angle.

Secondary glaucoma is caused by another disorder which functionally interferes with the outflow of aqueous humor or the flow from the posterior to the anterior chamber. Such

interference may be caused by inflammation, a tumor, an enlarged cataract, central retinal vein occlusion, trauma, or hemorrhage.

Several classes of drugs acting by different mechanisms are used as topically administered ocular therapy to lower IOP. These include beta adrenergic blockers (e.g., timolol), topical carbonic anhydrase inhibitors (e.g., dorzolamide), and α_2 -adrenergic receptor agonists (e.g., clonidine derivatives), all of which act primarily by decreasing the formation of aqueous humor within the eye. Pilocarpine and epinephrine are clinical agents that also lower IOP in glaucomatous eyes, but these drugs act principally by decreasing the resistance in the trabecular meshwork outflow channels. A third mechanism for lowering IOP in the primate eye is by increasing the outflow of aqueous humor via the uveoscleral route. Recently, a prostaglandin derivative belonging to the F2 α series of prostanoids, which acts primarily by this uveoscleral mechanism, has been introduced for glaucoma therapy. This drug, called latanoprost, is the isopropyl ester of a compound having the following structure:



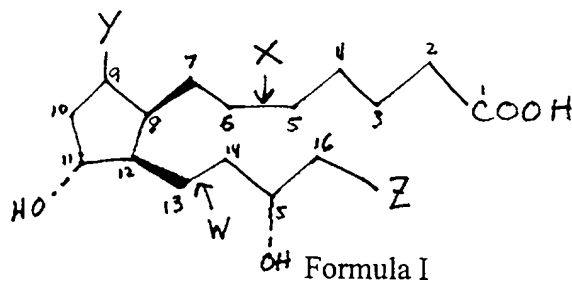
Prostaglandins which may be used in the treatment of glaucoma are described in United States Patents Nos. 5,476,872 by Garst et al., 4,599,353 by Bito, 5,262,437 by Chan, 5,462,968 by Woodward, 4,132,847 by Kuhla, 5,173,507 by DeSantis et al., 5,578,618 by Stjernschantz et al., 5,208,256 by Ueno, 5,565,492 by DeSantis et al., 5,151,444 by Ueno et al., and PCT Application No. PCT/US93/10853, International Publication No. WO 94/11002 by

Woodward.

The present invention relates to prostaglandins which are structurally different from latanoprost and other prostaglandins used in the treatment of glaucoma, and that belong to the 8-iso series of prostanoids, for example 8-iso PGE₁, 8-iso PGE₂ and 8-iso-PGF_{2α}. In contrast to latanoprost, 8-isoPGE₂ lowers IOP primarily by decreasing the resistance to trabecular outflow of aqueous humor from the eye.

SUMMARY OF THE INVENTION

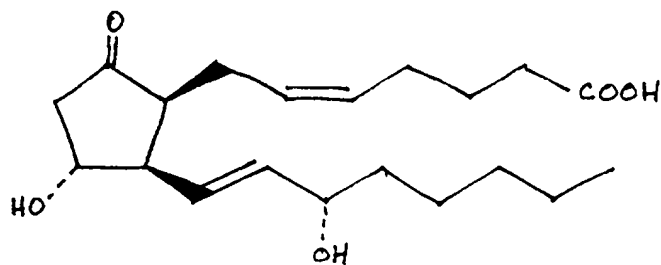
The present invention relates to the use of 8-iso prostanoids in methods which decrease intraocular pressure ("IOP") in the eye, for example in the treatment of glaucoma. The 8-iso-prostanoids of the invention have a common structure according to formula I:



where either bond W or bond X can be a single or a double bond, Y is either (i) a hydroxyl group having either α or β orientation relative to the five-membered ring or (ii) a keto function at carbon 9, and Z is a hydrocarbon group which may be aliphatic (cyclic or non-cyclic), aromatic, or a combination of aliphatic and aromatic at carbon 16.

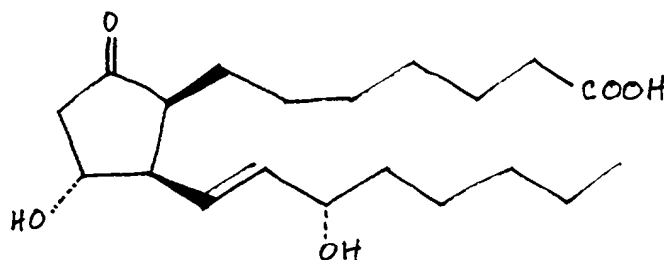
In a first nonlimiting embodiment of the invention, the 8-iso prostanoid is 8-iso prostaglandin E₂ (prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo, (5Z, 8 β , 11 α ,

13E,15S), having Formula II:



Formula II.

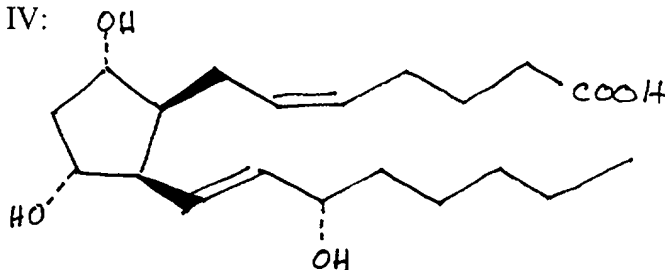
In a second nonlimiting embodiment of the invention, the 8-iso prostanoid is 8-iso, 5,6 dihydro prostaglandin E₂ (referred to as 8-iso PGE₁), having Formula III:



Formula III.

In a third nonlimiting embodiment of the invention, the 8-iso prostanoid is 8-iso PGF_{2α} (prosta-5,13-dien-1-oic acid, 9, 11, 15-trihydroxy-, (5Z, 8β, 9α, 11α, 13E, 15S)-, having

Formula IV:



Formula IV.

The present invention also provides for derivatives of compounds of Formulas II, III or IV which retain basic Formula I and their use in methods of decreasing intraocular pressure.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the use of 8-iso prostanoids having basic Formula I to decrease intraocular pressure in a subject in need of such treatment. In specific nonlimiting embodiments of the invention, the 8-iso prostanoid may be selected from the group of (i) 8-iso prostaglandin E₂ (prosta-5,13-dien-1-oic acid, 11,15-hydroxy-9-oxo, (5Z, 8β, 11α, 13E,15S) ("8-iso PGE₂"), having Formula II; (ii) the 5,6 dihydro derivative of 8-iso PGE₂, having Formula III and referred to as 8-iso PGE₁; (iii) prosta-5,13-dien-1-oic acid, 9, 11, 15-trihydroxy-, (5Z, 8β, 9α, 11α, 13E, 15S) ("8-iso PGF_{2α}"), having Formula IV; and (iv) derivatives of compounds having Formulas II, III or IV which retain basic Formula I and which, when administered to the eye of a subject having increased intraocular pressures, will decrease intraocular pressure by at least 10 percent.

The main structural differences between the 8-iso prostanoids of the invention and latanoprost are the following: (i) the side chain substituents on the five-membered rings have the opposite geometric arrangement with respect to the plane of the ring (cis for the 8-iso prostanoids of the invention and trans for latanoprost); (ii) the five-membered ring has a keto or hydroxyl function at position 9 in the 8-iso prostanoids of the invention, whereas there is just a hydroxyl group in the same position in latanoprost; and (iii) the side chains beginning with the sixteenth carbon may have different structures, as, for example, latanoprost containing a terminal methyl phenyl group at this position. 8-iso prostanoid derivatives of the invention contain a five-membered ring and two side chains, and retain distinguishing features (i)-(iii) as set forth in the preceding sentence and in Formula I. In preferred embodiments, such derivatives are esters of

compounds having Formula II, III or IV. For example, esterified derivatives of 8-iso PGE₂ may be used according to the invention, and may provide improved penetration into the eye.

The mechanism of action by which 8-iso PGE₂ lowers IOP has been found to be different from that of latanoprost in experiments done in primates, in that 8-iso PGE₂ has been found to increase trabecular outflow facility by decreasing resistance to outflow of aqueous humor. This is an advantage in that the trabecular meshwork is the primary locus of the pathology causing increased IOP in primary open angle glaucoma.

Accordingly, the present invention provides for a method for decreasing IOP comprising administering a therapeutically effective amount of an 8-iso prostanoid of the invention to a subject in need of such treatment. Such a method may be used in the treatment of glaucoma in a subject. Suitable formulations include for example, and not by way of limitation, a topical solution which is a physiological saline solution, having a pH between about 4.5 and 8 and an appropriate buffer system (e.g., acetate buffers, citrate buffers, phosphate buffers, borate buffers) a neutral pH being preferred. The formulation may further comprise a pharmaceutically acceptable preservative (e.g. benzalkonium chloride, thimerosal, chlorobutanol), stabilizer and/or surfactant (e.g. Tween 80). The formulation may also comprise a compound which acts as an anti-oxidant (e.g. sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole, butylated hydroxytoluene). A "therapeutically effective amount" of an 8-iso prostanoid of the invention refers to an amount of drug which decreases the IOP by at least about 10 percent, preferably at least about 15 percent, and more preferably at least about 20 percent. In particular embodiments of the invention, the administration of 8-iso prostanoid results

in an increase in trabecular outflow facility of at least about 10 percent, preferably at least about 20 percent, and more preferably at least about 30 percent. In nonlimiting embodiments of the invention, a topical preparation of 8-iso prostanoid at a concentration of between .001 and 1 percent, preferably between .005 and .2 percent, and more preferably between about .05 and .1 percent may be used.

According to the invention, IOP may be decreased, and/or glaucoma may be treated, using compositions comprising an 8-iso prostanoid of the invention as the sole active agent, or in conjunction with another active agent. For example, combinations of 8-iso prostanoid and another drug used to treat elevated intraocular pressure, including but not limited to another prostaglandin derivative (including, but not limited to, latanoprost), pilocarpine, epinephrine, a beta adrenergic agent (e.g., timolol), a carbonic anhydrase inhibitor (e.g., dorzolamide), or an α_2 -adrenergic receptor agonist (e.g., a clonidine derivative), may be used.

EXAMPLE I

Experiments were performed to evaluate the effects of single dose administration of 8-iso PGE₂ on IOP in normal ("N") and glaucomatous ("G") monkey eyes, and to determine the mechanism by which 8-iso PGE₂ alters IOP in N monkey eyes, when applied topically. A single 25 μ l dose study was performed in 6 N and 8 G monkeys. IOP and pupil sizes were measured before and at 0 hr, 0.5 hr and then hourly for a total of 6 hrs after 0.05% or 0.1% drug concentrations were administered. Tonographic outflow facility ("C") and fluorophotometric aqueous humor flow (F) were determined in 6 N monkeys before and after unilateral application

of 25 μ l of 0.1% 8-iso PGE₂. In 8 G monkey eyes, 8-isoPGE₂ reduced IOP ($p < 0.005$) up to 2 hrs or 5 hrs following administration of the 0.05% or 0.1% concentration, respectively. The maximum reduction in IOP was 4.6 ± 0.8 (mean \pm SEM) mm Hg (0.05%) and 6.6 ± 0.8 mm Hg (0.1%), as compared to baseline measurements. After topical application of 8-iso PGE₂ the IOP was lower ($p < 0.01$) in the treated eyes of 6 N monkeys for 4 hrs, with a maximum difference of 3.2 ± 0.2 mmHg, as compared to the fellow contralateral control eyes. The pupil size was smaller ($p < 0.01$) for 4 hrs, up to 1.0 ± 0.2 mm. Compared with vehicle-treated contralateral control eyes, C was greater ($p < 0.005$) by 48% at 2 hr after a single dose of 0.1% 8-iso PGE₂. F was unchanged ($p < 0.10$) over a period of 4 hrs after drug administration. Mild eyelid edema, conjunctival edema, hyperemia, and discharge appeared in some eyes treated with the 0.1% concentration.

Table 1A shows that 8-iso PGE₂ administered to the normal monkey eye lowers IOP significantly by 20.3% and increases outflow facility by 43.1%, an amount sufficient to account for the fall of IOP. By contrast, in Table 1B latanoprost in the normal monkey eye also lowers IOP significantly (by 10.8%), but the drug has no significant effect on outflow facility. The lack of a major effect on outflow facility of latanoprost in the primate eye is in agreement with studies in the literature by other investigators.

Table 1

A. Effect of 0.1% 8-isoPGE₂ on Outflow Facility in 6 Normal Monkeys

(2 hours after treatment)

	Intraocular Pressure Mean±SEM mmHg	Outflow Facility Mean±SEM μl/ml/mmHg
Treated eyes (drug)	13.0±0.7*	0.83±0.10*
Baseline	16.3±1.1	0.58±0.03
Control eyes (vehicle)	15.7±0.5	0.56±0.06
Baseline**	15.7±0.6	0.51±0.04

B. Effect of 0.005% latanoprost on Outflow Facility in 6 Normal Monkeys
(1 hour after treatment)

	Intraocular Pressure Mean±SEM mmHg	Outflow Facility Mean±SEM μl/min/mmHg
Treated eyes (drug)	13.2±0.7*	0.76±0.08
Baseline	14.8±0.7	0.62±0.07
Control eyes (vehicle)	15.0±0.8	0.60±0.07
Baseline**	15.7±0.3	0.73±0.08

*Significantly different as compared with either baseline values or vehicle-treated eyes (two-tailed paired t-test, p.<0.05).

** Baseline measurements made in the same monkeys at the same time one day prior to drug treatments

Table 2 shows the effect of 8-iso PGE₂ on IOP and outflow facility in

glaucomatous monkey eyes. Because of the individual variability in laser-induced glaucomatous monkey eyes, the IOP and facility measurements are expressed in the table as ratios (value of the drug-treated eye \div the value of the vehicle-treated eye). The ratios were calculated from the values of the same glaucomatous monkey eye determined immediately prior to administration of the drug or the vehicle (time 0 hrs.), and the values at 2 hours after administration of the drug or vehicle. The data in Table 2 show that in the primate, administration of 8-iso PGE₂ to glaucomatous eyes significantly lowers IOP (by 13.8%) and significantly increases outflow facility (by 38.8%), which is of sufficient magnitude to account for the fall in IOP. Thus the mechanism of lowering IOP by 8-iso PGE₂ in both normal and glaucomatous eyes is primarily due to an increase in aqueous humor trabecular outflow.

Table 2.

Effect of 0.1% 8-iso PGE₂ on IOP and Outflow Facility Responses
in 8 Glaucomatous Monkey Eyes (Unilateral)

Time	Intraocular Pressure (drug-treated/vehicle-treated)		Outflow facility (drug-treated/vehicle treated)	
	0 hr	2 hr	0 hr	2 hr
Response Ratio (\pm SEM)	0.976 \pm 0.002	0.843* \pm 0.0498	1.041 \pm 0.0498	1.445** \pm 0.161
% Change by drug	---	13.8 % decrease	---	38.8% increase

Significantly different as compared to 0 hr, paired t-test, $p < 0.01^*$, $< 0.10^{**}$

EXAMPLE II.

IOP was measured one hour before and at intervals up to six hours after a single

dose of 8-iso PGE₁ (the 13, 14 dihydro derivative of 8-iso PGE₂), 8-iso PGE₂, or 8-iso PGF_{2α} in laser-induced glaucomatous eyes in cynomolgus monkeys (wherein only one eye is rendered glaucomatous and the other serves as a control). Following one day of baseline IOP measurement, a single 25 µl dose of either (i) 0.1 percent 8-iso PGE₁, or (ii) 0.1 percent 8-iso PGE₂, or (iii) 0.1 percent 8-iso PGF_{2α}, was topically applied to the glaucomatous eye in groups of 4 or 8 monkeys. It was found that 8-iso PGE₁ (0.1 percent) reduced IOP (p<0.05) for up to four hours in glaucomatous monkey eyes (n=4). The maximum reduction in IOP was 5.3 ± 0.8 (mean ± SEM) mm Hg at 2 hours after dosing. 8-iso PGE₂ (0.1 percent) reduced IOP (p<0.05) for 5 hours with a maximum reduction in IOP of 6.6 ± 0.8 mm Hg at 2 hours after dosing (n=8). After 0.1 percent 8-iso PGF_{2α}, a significant (p<0.05) reduction in IOP occurred only at 1 hour with the maximum reduction in IOP of 3.3 ± 0.9 mm Hg (n=4). The results are shown in Table 3. Based on these studies, of the compounds tested, 8-iso PGE₂ appears to have the greatest and 8-iso PGF_{2α} the least activity in decreasing IOP in glaucomatous monkey eyes.

Table 3.
Intraocular Pressure (treated - baseline) (mean mm Hg ± SEM)

iso PG, 0.1%	n	1 hr	2 hr	4 hr	6 hr
8-iso PGE ₁	4	-3.3 ± 1.3	-5.3 ± 0.8*	-2.3 ± 0.5*	-1.3 ± 0.9
8-iso PGE ₂	8	-4.5 ± 0.9**	-6.6 ± 0.8**	-2.9 ± 0.6**	-1.2 ± 1.2
8-iso PGF _{2α}	4	-3.3 ± 0.8*	-1.8 ± 1.1	-0.8 ± 1.7	0.3 ± 0.5

* p<0.05

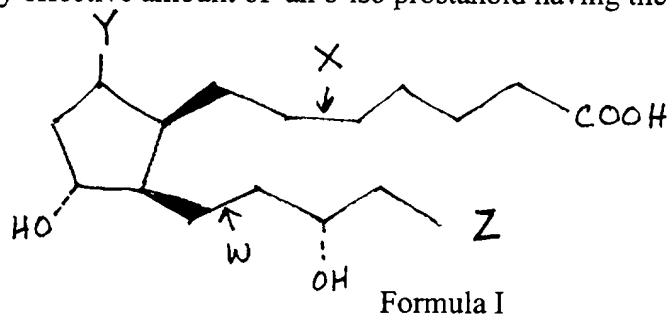
** p<0.005

Various publications are cited herein, the contents of which are hereby
incorporated by reference in their entireties.

2025 RELEASE UNDER E.O. 14176

WE CLAIM:

1. A method for decreasing intraocular pressure comprising administering a therapeutically effective amount of an 8-iso prostanoid having the following Formula I:

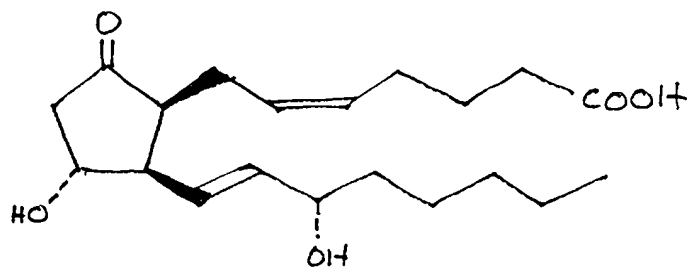


where bond W is selected from the group consisting of a single covalent bond and a double covalent bond, bond X is selected from the group consisting of a single covalent bond and a double covalent bond, substituent Y is selected from the group consisting of a hydroxyl group having either α or β orientation relative to the five-membered ring and a keto function, and substituent Z is a hydrocarbon group selected from the group of aliphatic, aromatic, or a combination of aliphatic and aromatic hydrocarbon, to a patient in need of such treatment.

2. The method of claim 1 wherein the 8-iso prostanoid is administered topically.

3. The method of claim 2 wherein the 8-iso prostanoid is administered as a composition comprising between .005 to 1 percent 8-iso prostanoid.

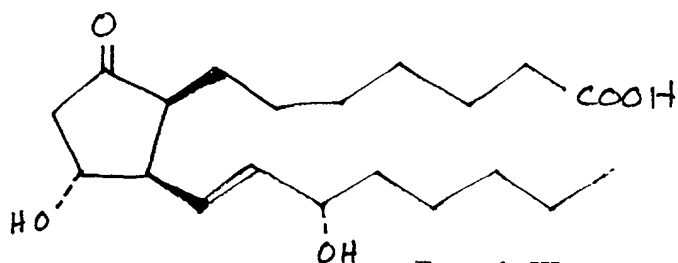
4. The method of claim 1, wherein the 8-iso prostanoid is selected from the group consisting of a compound having the following Formula II



Formula II

or a derivative thereof.

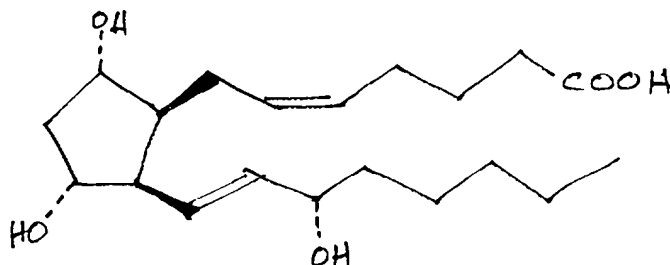
5. The method of claim 1, wherein the 8-iso prostanoid is selected from the group consisting of a compound having the following Formula III



Formula III

or a derivative thereof.

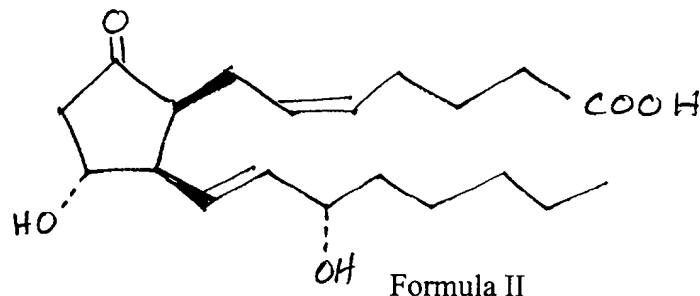
6. The method of claim 1, wherein the 8-iso prostanoid is selected from the group consisting of a compound having the following Formula IV



Formula IV

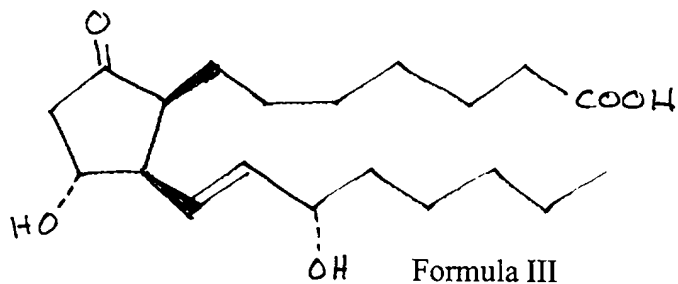
or a derivative thereof.

7. The method of claim 2, wherein the 8-iso prostanoic acid is selected from the group consisting of a compound having the following Formula II



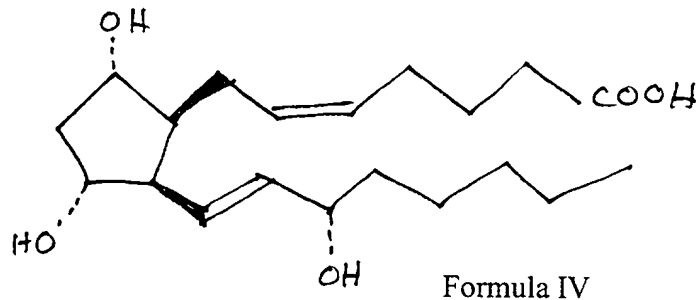
or a derivative thereof.

8. The method of claim 2, wherein the 8-iso prostanoic acid is selected from the group consisting of a compound having the following Formula III



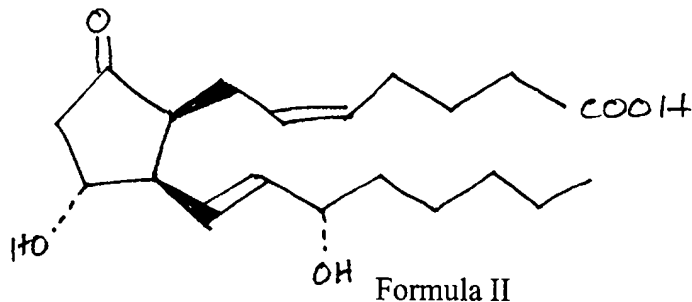
or a derivative thereof.

9. The method of claim 2, wherein the 8-iso prostanoic acid is selected from the group consisting of a compound having the following Formula IV



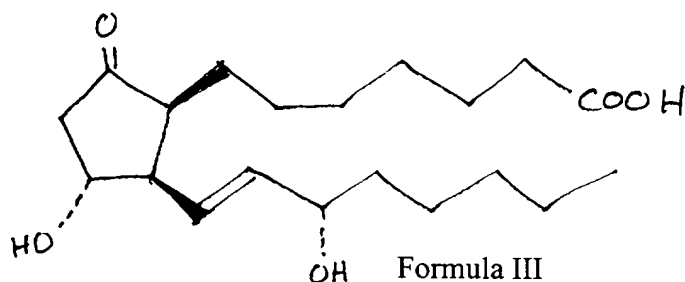
or a derivative thereof.

10. The method of claim 3, wherein the 8-iso prostanoid is selected from the group consisting of a compound having the following Formula II



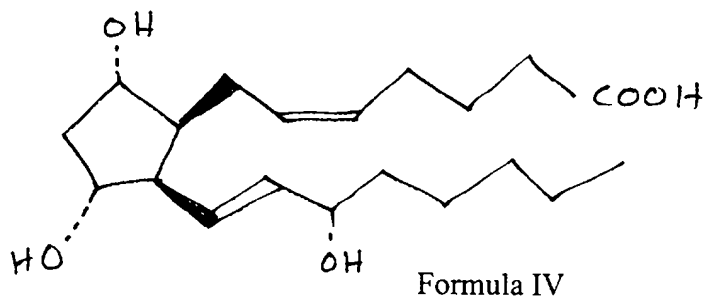
or a derivative thereof.

11. The method of claim 3, wherein the 8-iso prostanoid is selected from the group consisting of a compound having the following Formula III



or a derivative thereof.

12. The method of claim 3, wherein the 8-iso prostanoid is selected from the group consisting of a compound having the following Formula IV



or a derivative thereof.

13. The method of claim 4, wherein the derivative is an ester derivative.
14. The method of claim 5, wherein the derivative is an ester derivative.
15. The method of claim 6, wherein the derivative is an ester derivative.
16. The method of claim 7, wherein the derivative is an ester derivative.
17. The method of claim 8, wherein the derivative is an ester derivative.
18. The method of claim 9, wherein the derivative is an ester derivative.
19. The method of claim 10, wherein the derivative is an ester derivative.
20. The method of claim 11, wherein the derivative is an ester derivative.
21. The method of claim 12, wherein the derivative is an ester derivative.

ABSTRACT

The present invention relates to the use of 8-iso prostaglandins and their derivatives for decreasing intraocular pressure, for example in the treatment of glaucoma. It is based, at least in part, on the discovery that 8-iso prostaglandin E₂ effectively decreased intraocular pressure by a trabecular meshwork outflow mechanism.

**COMBINED DECLARATION
AND POWER OF ATTORNEY**

(Original, Design, National Stage of PCT, Divisional, Continuation or C-I-P Application)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

8-ISO PROSTAGLANDINS FOR GLAUCOMA THERAPY This declaration is of the following type:

- ☐ original
- ☐ design
- ☐ national stage of PCT.
- ☐ divisional
- ☐ continuation
- ☒ continuation-in-part (C-I-P)

the specification of which: *(complete (a), (b), or (c))*

- (a) ☒ is attached hereto.
- (b) ☐ was filed on as Application Serial No. and was amended on *(if applicable)*.
- (c) ☐ was described and claimed in PCT International Application No. filed on and was amended on *(if applicable)*.

Acknowledgement of Review of Papers and Duty of Candor

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of the subject matter claimed in this application in accordance with Title 37, Code of Federal Regulations § 1.56.

☐ In compliance with this duty there is attached an information disclosure statement. 37 CFR 1.98.

Priority Claim

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT International Application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT International Application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application on which priority is claimed

(complete (d) or (e))

- (d) ☐ no such applications have been filed.
- (e) ☐ such applications have been filed as follows:

PRIOR FOREIGN/PCT APPLICATION(S) FILED WITHIN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION			
COUNTRY	APPLICATION NO	DATE OF FILING (day, month, year)	DATE OF ISSUE (day, month, year)
			PRIORITY CLAIMED UNDER 35 USC 119 [] YES NO []
			[] YES NO []
			[] YES NO []
ALL FOREIGN APPLICATION(S), IF ANY, FILED MORE THAN 12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO SAID APPLICATION			
			[] YES NO []
			[] YES NO []
			[] YES NO []

Claim for Benefit of Prior U.S. Provisional Application(s)

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below:

Provisional Application Number	Filing Date

Claim for Benefit of Earlier U.S./PCT Application(s) under 35 U.S.C. 120

(complete this part only if this is a divisional, continuation or C-I-P application)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information as defined in Title 37, Code of Federal Regulations, § 1.56 which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

08/853,803 May 9, 1997 pending
(Application Serial No.) (Filing Date) (Status) (patented, pending, abandoned)

(Application Serial No.) (Filing Date) (Status) (patented, pending, abandoned)

Power of Attorney

As a named inventor, I hereby appoint Dana M. Raymond, Reg. No. 18,540; Frederick C. Carver, Reg. No. 17,021; Francis J. Hone, Reg. No. 18,662; Joseph D. Garon, Reg. No. 20,420; Arthur S. Tenser, Reg. No. 18,839; Ronald B. Hildreth, Reg. No. 19,498; Thomas R. Nesbitt, Jr., Reg. No. 22,075; Robert Neuner, Reg. No. 24,316; Richard G. Berkley, Reg. No. 25,465; Richard S. Clark, Reg. No. 26,154; Bradley B. Geist, Reg. No. 27,551; James J. Maune, Reg. No. 26,946; John D. Murnane, Reg. No. 29,836; Henry Tang, Reg. No. 29,705; Robert C. Scheinfeld, Reg. No. 31,300; John A. Fogarty, Jr., Reg. No. 22,348; Louis S. Sorell, Reg. No. 32,439 and Rochelle K. Seide, Reg. No. 32,300 of the firm of BAKER & BOTTS, L.L.P., with offices at 30 Rockefeller Plaza, New York, New York 10112, as attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith

SEND CORRESPONDENCE TO: BAKER & BOTTS, L.L.P. 30 ROCKEFELLER PLAZA, NEW YORK, N.Y. 10112 CUSTOMER NUMBER: 21003	DIRECT TELEPHONE CALLS TO: BAKER & BOTTS, L.L.P. (212) 705-5000
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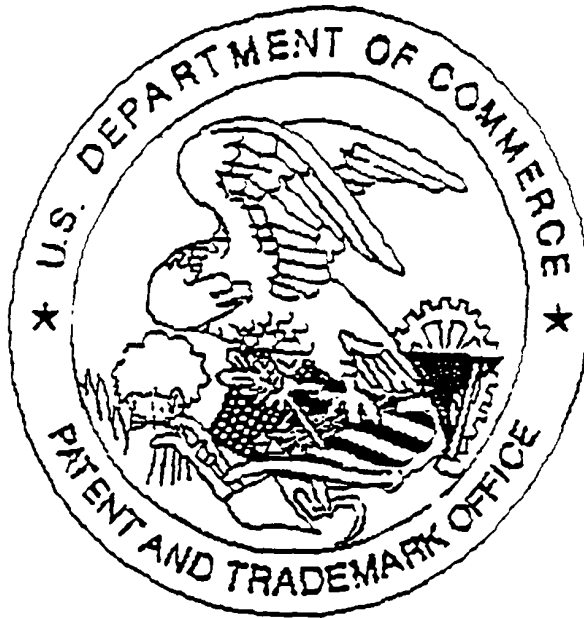
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section

1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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DATE	SIGNATURE OF INVENTOR			

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